

Gene of the issue – RUNX1 mutations and inherited bleeding

Morgan, Neil; Daly, Martina E

DOI:

[10.1080/09537104.2017.1280151](https://doi.org/10.1080/09537104.2017.1280151)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Morgan, N & Daly, ME 2017, 'Gene of the issue – RUNX1 mutations and inherited bleeding', *Platelets*, vol. 28, no. 2, pp. 208-210. <https://doi.org/10.1080/09537104.2017.1280151>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



Gene of the issue: RUNX1 mutations and inherited bleeding

Neil V. Morgan & Martina E. Daly

To cite this article: Neil V. Morgan & Martina E. Daly (2017): Gene of the issue: RUNX1 mutations and inherited bleeding, Platelets, DOI: [10.1080/09537104.2017.1280151](https://doi.org/10.1080/09537104.2017.1280151)

To link to this article: <http://dx.doi.org/10.1080/09537104.2017.1280151>



© The Author(s). Published by Taylor & Francis.



Published online: 17 Feb 2017.



Submit your article to this journal [↗](#)



Article views: 31



View related articles [↗](#)



View Crossmark data [↗](#)

GENE OF THE ISSUE

Gene of the issue: *RUNX1* mutations and inherited bleeding

Neil V. Morgan¹ & Martina E. Daly²

¹Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK and ²Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

Keywords

Bleeding, inherited mutations, platelets, *RUNX1* gene

History

Received 22 December 2016, Accepted 28 December 2016, Published online 17 February 2017

Familial platelet disorder with predisposition to acute myelogenous leukemia (FPD/AML) (OMIM #601399) is an autosomal dominant disorder characterized by quantitative and qualitative platelet defects and an increased risk of AML. FPD/AML shares phenotypic similarities with Jacobsen syndrome; platelet counts show mild to moderate reductions but are variable between individuals with the same genetic etiology of disease, and a reduction in dense granule secretion is often observed as a secondary qualitative abnormality [1]. The major clinical complication of this disorder, however, is not the bleeding tendency experienced by some patients, but the propensity for a proportion of patients to develop myelodysplasia or leukemia [2].

The molecular genetic cause of FPD/AML was first elucidated by linkage studies which mapped the underlying genetic defect to a region on human chromosome 21q [3]. Contained within this region is the gene encoding the master regulator of hematopoiesis, Runt-related transcription factor 1 (*RUNX1*). Variants have been identified throughout the coding region of *RUNX1* but those clustered within the region encoding the Runt homology domain (RHD), which mediates DNA binding and heterodimerization with core binding factor beta (CBF- β) [4], and are most likely to be detrimental [5]. *RUNX1* mutation can result in haploinsufficiency of *RUNX1*, or reduced *RUNX1* function as a result of a dominant-negative effect, that disrupts the formation of complexes with CBF- β , thereby disturbing the regulation of genes necessary for hematopoietic stem cell (HSC) maintenance, maturation, and differentiation [6,7].

Over 40 *RUNX1* mutations associated with FPD/AML have been reported in patients to date (Table I, Figure 1). However, the prevalence of *RUNX1* defects is believed to be underestimated and as sequencing technologies improve an increasing number of patients are being reported [8,9]. The mutations reported are predominantly missense and phenotypically platelets from patients present with dense granule secretion defects and persistence of MYH10 expression which can be used as a biomarker of genetic variation [1,10]. It has been suggested that the risk of malignancy is reduced in those cases having *RUNX1* defects that cause haploinsufficiency when compared to those patients with dominant-negative *RUNX1* defects. Due to the associated predisposition to myeloid malignancy with some variants in *RUNX1*, it is critical to establish diagnosis as early as possible to aid in patient management and guidance.

Main findings

- *RUNX1* defects are associated with mild to moderately reduced platelet counts.
- *RUNX1* defects are associated with reduced responses to several platelet agonists and decreased platelet secretion.
- *RUNX1* missense mutations are almost exclusively located in the Runt homology DNA-binding domain.
- *RUNX1* defects causing haploinsufficiency are thought to be associated with a lower incidence of myeloid malignancies when compared to those patients with dominant-negative *RUNX1* defects.

Declaration of interest

The authors report no conflict of interest.

Funding

The work in the author's laboratories is supported by the British Heart Foundation (PG/13/36/30275; FS/15/18/31317).

Correspondence: Dr. Neil V. Morgan, Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

E-mail: n.v.morgan@bham.ac.uk

© Neil V. Morgan and Martina E. Daly. Published with license by Taylor & Francis.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table I. *RUNX1* variants reported to date in patients with an FPD/AML inherited bleeding disorder. Heterozygous *RUNX1* nucleotide changes present in patients with inherited bleeding and their predicted effects on the resulting RNA or protein are also shown. Genomic variations are numbered according to positions in the NM_001001890 transcript for *RUNX1*. The references where they were initially reported is also indicated.

Genomic variation	Protein effect	Variation type	References
c.16 G>A	p.D6N	Missense	[9]
c.82dup888	p.A28GfsX83	Insertion	[11]
c.236 G>A	p.W79X	Nonsense	[1]
c.239 G>A	p.R80H	Missense	[8]
c.247 A>G	p.K83E	Missense	[12]
c.270+1G>T		Splicing	[1,9]
c.271-1G>T		Splicing	[3]
c.295 G>C	p.D99H	Missense	[11]
c.319 G>C	p.A107P	Missense	[2]
c.322 G>A	p.G108S	Missense	[9]
c.361_368delACCGCAGC	p.T121HfsX9	Deletion	[8,13]
c.386 C>A	p.A129E	Missense	[8,14]
c.415 C>T	p.R139X	Nonsense	[15]
c.416 G>A	p.R139Q	Missense	[3]
c.426delA	p.Ser145AfsX4	Deletion	[16]
c.427 G>A	p.G143R	Missense	[17]
c.427+1G>T		Splicing	[1]
c.428+3delA	p.R135fsX177	Splicing	[12]
c.505 A>G	p.T169A	Missense	[9]
c.506 C>G	p.T169R	Missense	[8]
c.511 G>T	p.D171Y	Missense	[17]
c.512 A>T	p.D171V	Missense	[9]
c.520 C>T	p.R174X	Nonsense	[3]
c.521 G>A	p.R174Q	Missense	[3,8]
c.529 C>T	p.R177X	Nonsense	[3]
c.530 G>A	p.R177Q	Missense	[8,9,14]
c.568 G>A	p.G190R	Missense	[18]
c.654delC	p.T219RfsX8	Deletion	[19]
c.703 C>T	p.Q235X	Nonsense	[17]
c.707delC	p.P236LfsX48	Deletion	[20]
c.780 C>A	p.Y260X	Nonsense	[12]
c.786delA	p.S263PfsX21	Deletion	[21]
c.877 C>T	p.R293X	Nonsense	[11]
c.906delG	p.F303SfsX264	Deletion	[22]
c.918_922dup	p.Q308RfsX261	Insertion	[8,14]
c.1007_1013delGCATCGG	p.G336AfsX229	Deletion	[11]
c.1011delC	p.I337MfsX230	Deletion	[8]
c.1082 C>A	p.S361X	Nonsense	[23]

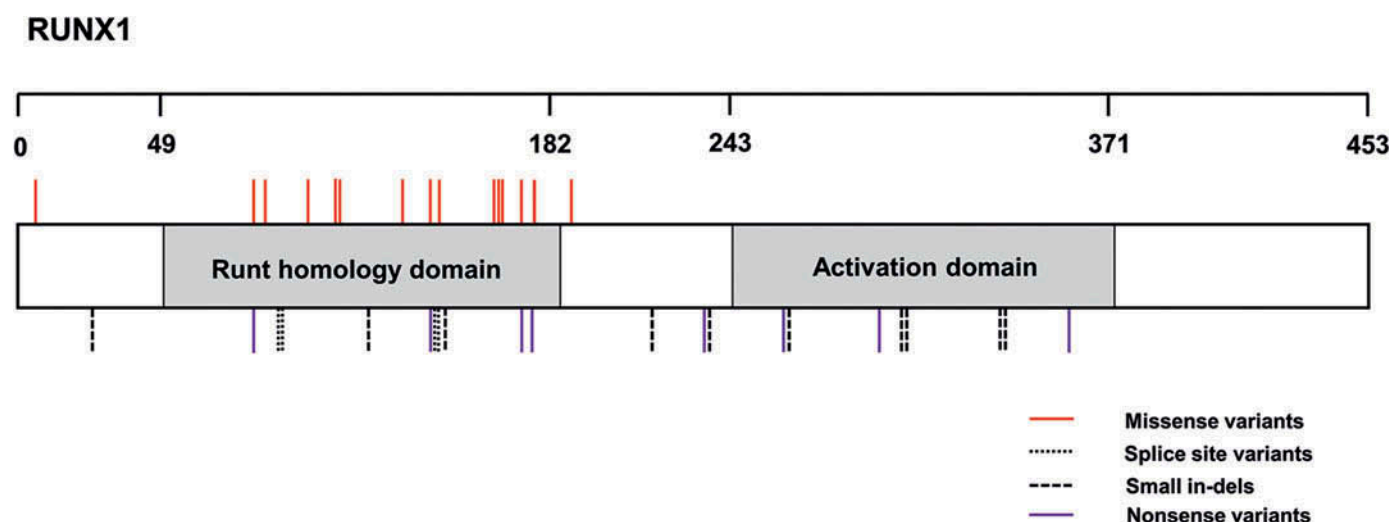


Figure 1. Schematic showing the protein location of all previously published variants within *RUNX1* which are implicated in FPD/AML. The Runt-homology DNA-binding domain spanning amino acids 49 to 182 and the Activation domain spanning from amino acid 243 to 371 is also displayed. Alterations are numbered according to positions in the NM_001001890 transcript for *RUNX1*.

References

1. Stockley J, Morgan NV, Bem D, Lowe GC, Lordkipanidze M, Dawood B, Simpson MA, Macfarlane K, Horner K, Leo VC, et al. Enrichment of FLI1 and RUNX1 mutations in families with excessive bleeding and platelet dense granule secretion defects. *Blood* 2013 Dec 12;122(25):4090–4093.
2. Walker LC, Stevens J, Campbell H, Corbett R, Spearing R, Heaton D, Macdonald DH, Morris CM, Ganly P. A novel inherited mutation of the transcription factor RUNX1 causes thrombocytopenia and may predispose to acute myeloid leukaemia. *Br J Haematol* 2002 Jun;117(4):878–881.
3. Song WJ, Sullivan MG, Legare RD, Hutchings S, Tan X, Kufrin D, Ratajczak J, Resende IC, Haworth C, Hock R, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. *Nat Genet* 1999 Oct;23(2):166–175.
4. Kamachi Y, Ogawa E, Asano M, Ishida S, Murakami Y, Satake M, Ito Y, Shigesada K. Purification of a mouse nuclear factor that binds to both the A and B cores of the polyomavirus enhancer. *J Virol* 1990 Oct;64(10):4808–4819.
5. Johnson B, Lowe GC, Futterer J, Lordkipanidze M, MacDonald D, Simpson MA, Sanchez Guiu I, Drake S, Bem D, Leo V, et al. Whole exome sequencing identifies genetic variants in inherited thrombocytopenia with secondary qualitative function defects. *Haematologica* 2016 Jun 16.
6. Jalagadugula G, Mao G, Kaur G, Goldfinger LE, Dhanasekaran DN, Rao AK. Regulation of platelet myosin light chain (MYL9) by RUNX1: implications for thrombocytopenia and platelet dysfunction in RUNX1 haploinsufficiency. *Blood* 2010 Dec 23;116(26):6037–6045.
7. Hart SM, Foroni L. Core binding factor genes and human leukemia. *Haematologica* 2002 Dec;87(12):1307–1023.
8. Latger-Cannard V, Philippe C, Bouquet A, Baccini V, Alessi MC, Ankri A, Bauters A, Bayart S, Cornillet-Lefebvre P, Daliphard S, et al. Haematological spectrum and genotype-phenotype correlations in nine unrelated families with RUNX1 mutations from the French network on inherited platelet disorders. *Orphanet J Rare Dis* 2016 Apr 26;11:49.
9. Johnson B, Lowe GC, Futterer J, Lordkipanidze M, MacDonald D, Simpson MA, Sanchez-Guiu I, Drake S, Bem D, Leo V, et al. Whole exome sequencing identifies genetic variants in inherited thrombocytopenia with secondary qualitative function defects. *Haematologica* 2016 Oct;101(10):1170–1179.
10. Antony-Debre I, Bluteau D, Itzykson R, Baccini V, Renneville A, Boehlen F, Morabito M, Droin N, Deswarte C, Chang Y, et al. MYH10 protein expression in platelets as a biomarker of RUNX1 and FLI1 alterations. *Blood* 2012 Sep 27;120(13):2719–2722.
11. Owen CJ, Toze CL, Koochin A, Forrest DL, Smith CA, Stevens JM, Jackson SC, Poon MC, Sinclair GD, Leber B, et al. Five new pedigrees with inherited RUNX1 mutations causing familial platelet disorder with propensity to myeloid malignancy. *Blood* 2008 Dec 01;112(12):4639–4645.
12. Michaud J, Wu F, Osato M, Cottles GM, Yanagida M, Asou N, Shigesada K, Ito Y, Benson KF, Raskind WH, et al. In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. *Blood* 2002 Feb 15;99(4):1364–1372.
13. Beri-Dexheimer M, Latger-Cannard V, Philippe C, Bonnet C, Chambon P, Roth V, Gregoire MJ, Bordigoni P, Lecompte T, Leheup B, et al. Clinical phenotype of germline RUNX1 haploinsufficiency: from point mutations to large genomic deletions. *Eur J Hum Genet* 2008 Aug;16(8):1014–1018.
14. Preudhomme C, Renneville A, Bourdon V, Philippe N, Roche-Lestienne C, Boissel N, Dhedin N, Andre JM, Cornillet-Lefebvre P, Baruchel A, et al. High frequency of RUNX1 biallelic alteration in acute myeloid leukemia secondary to familial platelet disorder. *Blood* 2009 May 28;113(22):5583–5587.
15. Bluteau D, Gilles L, Hilpert M, Antony-Debre I, James C, Debili N, Camara-Clayette V, Wagner-Ballon O, Cordette-Lagarde V, Robert T, et al. Down-regulation of the RUNX1-target gene NR4A3 contributes to hematopoiesis deregulation in familial platelet disorder/acute myelogenous leukemia. *Blood* 2011 Dec 08;118(24):6310–6320.
16. Langabeer SE, Owen CJ, McCarron SL, Fitzgibbon J, Smith OP, O'Marcaigh A, Browne P. A novel RUNX1 mutation in a kindred with familial platelet disorder with propensity to acute myeloid leukaemia: male predominance of affected individuals. *Eur J Haematol* 2010 Dec;85(6):552–553.
17. Buijs A, Poot M, van der Crabben S, van der Zwaag B, van Binsbergen E, van Roosmalen MJ, Tavakoli-Yaraki M, de Weerd O, Nieuwenhuis HK, van Gijn M, et al. Elucidation of a novel pathogenomic mechanism using genome-wide long mate-pair sequencing of a congenital t(16;21) in a series of three RUNX1-mutated FPD/AML pedigrees. *Leukemia* 2012 Sep;26(9):2151–2154.
18. Linden T, Schnittger S, Groll AH, Juergens H, Rossig C. Childhood B-cell precursor acute lymphoblastic leukaemia in a patient with familial thrombocytopenia and RUNX1 mutation. *Br J Haematol* 2010 Dec;151(5):528–530.
19. Heller PG, Glembotsky AC, Gandhi MJ, Cummings CL, Pirola CJ, Marta RF, Kornblihtt LI, Drachman JG, Molinas FC. Low Mpl receptor expression in a pedigree with familial platelet disorder with predisposition to acute myelogenous leukemia and a novel AML1 mutation. *Blood* 2005 Jun 15;105(12):4664–4670.
20. Appelmann I, Linden T, Rudat A, Mueller-Tidow C, Berdel WE, Mesters RM. Hereditary thrombocytopenia and acute myeloid leukemia: a common link due to a germline mutation in the AML1 gene. *Ann Hematol* 2009 Oct;88(10):1037–1038.
21. Shiba N, Hasegawa D, Park MJ, Murata C, Sato-Otsubo A, Ogawa C, Manabe A, Arakawa H, Ogawa S, Hayashi Y. CBL mutation in chronic myelomonocytic leukemia secondary to familial platelet disorder with propensity to develop acute myeloid leukemia (FPD/AML). *Blood* 2012 Mar 15;119(11):2612–2614.
22. Kirito K, Sakoe K, Shinoda D, Takiyama Y, Kaushansky K, Komatsu N. A novel RUNX1 mutation in familial platelet disorder with propensity to develop myeloid malignancies. *Haematologica* 2008 Jan;93(1):155–156.
23. Churpek JE, Garcia JS, Madzo J, Jackson SA, Onel K, Godley LA. Identification and molecular characterization of a novel 3'; mutation in RUNX1 in a family with familial platelet disorder. *Leukemia Lymphoma* 2010 Oct;51(10):1931–1935.